RECEIVED
CENTRAL FAX CENTER
FEB 0 8 2007

Amendments to the Specification:

Please amend the specification as follows:

Please replace the paragraph at Page 119, line 22 to page 120, line 4 with the following:

One of the 6 new clones (SP4.6) from the SP1.2 L x H library differed more substantially from SP1.2 as well as from SP1.7-11. SP4.6 is a member of the VH1 family. However, it is more closely related to the germline gene hvlL1 (Olee, T., E.W. Lu, D-F. Huang, R.W. Soto-Gil, M. Deftos, F. Kozin, D.A. Carson, and P.P. Chen, "Genetic analysis of self-associating immunoglobulin G rheumatoid factors from two rheumatoid synovia implicates an antigen-driven response," J. Exp. Med. VOL. 1750:8310 (1992)) (88% homology) ~~(Fig. 31A and B)~~ than to 1-1. The D region does not resemble any published D region sequence ~~(Fig. 31 C)~~. The SP4.6 J region is a JH4 truncated at its 5' end. The most surprising finding was that the hinge region sequence indicates that SP4.6 is an IgG4, in contrast to SP1.2 and SP1.7-11 which are IgGI. The C region primer used for PCR in constructing the SP H chain library ("CH1"; Stratacyte, San Diego CA) is described as an IgG1 primer with the capacity to cross-prime with other IgG subclasses.

Please replace the paragraph at Page 120, line 5 to line 20 with the following:

TPO binding clones from the SPI.2 H x L library. The nucleotide sequences of the L chains were determined in 11 TPO-binding clones in the SP1.2 H x L library. At the amino acid level, the V kappa regions of 9 clones were very similar to, and 2 clones (SP1.17 and SPI.19) were identical to, the original SP1.2 L chain ~~(Fig. 32A)~~. Four of the 9 clones (SP1.14, -15, -21 and -22) have identical V kappa regions. All 11 new L chain clones appear to be derived from the V kappa germline gene HUMIGKLVJ (GenBank accession number D90158), as described above for SP1.2. At the amino acid level, all 11 are.more homologous with HUMIGKLVJ (83% for SP1.18 to 92% for SP1.20) than is SP1.2 (81%). The J kappa regions of 10 of the 11 new clones belong to JK1 or JK2 ~~(Fig. 32B)~~. The J kappa region of SP1.21 has not been assigned. SP1.14,

SP1.15 and SP1.22 have identical V kappa and J kappa sequences. Because clones SP1.17 and SP1.19 have JK2 regions (like SPL2) these clones are, overall, identical to SP1.2.

Please replace the paragraph at Page 120, line 30, to page 121, line 6 with the following:

Binding domains on TPO for SP F(ab)s. To determine whether or not there was overlap in the domains on TPO recognized by SP4.6, SP1.20 and SP1.2, studies with an immobilized SPI.2 F(ab) were performed. As expected, pre-incubation of ^{125}I- TPO with increasing concentrations of free SP1.2 inhibited the subsequent binding of the antigen to the immobilized SP1.2 ~~(Fig. 33)~~ **(Fig. 26)**. The SP4.6 and SP1.20 F(ab)s were equally effective, indicating that the binding domains of all 3 F(ab)s overlapped. No competition was observed with another anti-TPO F(ab) cloned from another patient.

Please replace the paragraph at Page 131, line 8 to 18 with the following:

TPO-specific F(ab) gene usage: Analysis of the presumptive germline genes used for 34 TPO human autoantibodies revealed the use of relatively restricted numbers and combinations of H and L chain genes (Table VI; ~~Figs. 34 and 35~~). In particular, L chain germline gene HUMIGKLVJ is used in TPO autoantibodies from all 4 patients. In 3 patients, HUMIGKLVJ was the only L chain obtained. In one patient (TR), 2 other TPO-specific L chains were obtained; A' is a VK1 (like HUMIGKLVJ) and A3 is a VK2. Of interest is an apparent association between JK VH gene usage (see below). For example, in 2 different patients (WR and TR), the association of JK1 with HUMIGKLVJ is seen only with VH gene 3-1.

Please replace the paragraph at Page 131, line 19 to 30 with the following:

The TPO-specific F(ab) H usage was less restricted than that of the L chain. Seven different H chains were used, involving 5 VHI, 1 VH3 and 1 VH4 germline genes. The D regions

were all unique ~~(Fig. 34)~~. Three of the H chains (1-1, HVlLl and 3-1) are used in two patients. Each of these H chains is a member of the VH1 family and is used in combination with L chain germline gene HUMIGKLVJ. Four of the TPO-specific H chains were found only in individual patients (4.22, 8-1B, HV1263 and V35). Of these H chains, two were combined with L chain HUMIGKLVJ, 4.22 (a VH4) and 8-1B (a VH3). Out of a total of 7 H and L chain combinations, only 2 were unique for both their H and L chains (HV1263/A3 and V35/A').

Please replace the paragraph at Page 132, line 6 to 18 with the following:

Domains on TPO recognized by F(ab)s: Competition between pairs of F(ab)s for binding to human TPO was used to define their respective binding domains. In this approach, increasing concentrations of one F(ab) were pre-incubated with radiolabelled TPO and then added to a second, immobilized F(ab). Representative experiments are shown in **Fig. 27** ~~Fig. 36~~. For example (~~Fig. 36A~~ **Fig. 27A**), TR1.8 and TR1.9 each completely inhibited TPO binding to immobilized TR1.9. In contrast, pre-incubation of WR1.7 and SP1.5 with radiolabeled TPO did not prevent subsequent TPO binding to immobilized TR1.9. Despite these differences in their ability to compete for TPO binding to TR1.9, all free F(ab)s were capable of binding comparable amounts of radiolabeled TPO in separate, concurrent assays (~~Fig. 36B~~ **Fig. 27B**).

Please replace the paragraph at Page 132, line 19 to 28 to the following:

The above experiment (~~Fig. 36A and 36B~~ **Fig. 27A and 27B**) demonstrates overlap in the areas on TPO recognized by TR1.9 and TR1.8 but not between TR1.9 and WR1.7 or SP1.5. Similarly, there was overlap in the WT1.7 binding domain with those of TR1.8 and SP1.5 but not with TR1.9 (~~Fig. 36C~~ **Fig. 27C**). The SP1.5 binding domain overlapped that of TR1.3 and WR1.7 but not TR1.9 (Fig. 36D). The SP1.5 domain appeared to overlap to a small extent with that of TR1.8 (~~Fig. 36D~~ **Fig. 27D**). It is important to note that these differences between F(ab)

binding domains are not related to differences in their affinities for TPO (Table VII).

Please replace the paragraph at Page 132, line 29 to page 133, line 9 to the following:

Experiments covering all permutations of immobilized and free F(ab)s suggest that there are two domains, A and B, recognized on human TPO. The extent to which the F(ab)s interact with each domain is summarized in Table VIII and is shown schematically in ~~Fig. 37~~ Fig. 28. The binding sites, of SP1.5 and WR4.5 lie completely within the TPO A domain. TR1.9 binds entirely to the B domain. TR1.8 interacts predominantly with the B domain but overlaps slightly with the A domain. Conversely, WR1.7 binds primarily to the A domain but also overlaps with TR1.8 (but not TR1.9) in the B domain. The binding site of TR1.3 spans the A and B domains equally.

Please replace the paragraph at Page 133, line 7 to 26 to the following:

Domains on TPO recognized by autoantibodies in patients' sera: The question arises as to what extent the TPO binding domains A and B reflect the binding domains of TPO autoantibodies in patients' sera. F(ab)s WR1.7 and TR1.9 were selected for competition studies with serum TPO autoantibodies because their binding sites do not overlap yet extensively cover the A and B domains. A spectrum of competition patterns was observed in 10 randomly selected sera of patients with autoimmune thyroid disease. In the representative examples shown, TPO autoantibodies in patients' sera were inhibited preferentially by WR1.7 (~~Fig. 38A~~ Fig. 29A), preferentially by TR1.9 (~~Fig. 38B~~ Fig. 29B) or in a more balanced proportion by both F(ab)s (~~Fig. 38C~~ Fig. 29C). Overall, of the 10 sera, 5 were inhibited preferentially by WR1.7, 2 by TR1.9 and 3 to approximately the same extent by WR1.7 and TR1.9. Of greater importance was the efficacy of the combination of the WR1.7 and TR1.9 F(ab)s in competing for serum TPO autoantibody binding. In the 10 sera, this combination inhibited TPO autoantibody binding by 83

± 5 % (mean U± S.E.M.). These figures underestimate the full extent of the inhibition because of limitations to the highest concentrations of F(ab)s which could be used for competition.